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## REVIEW ARTICLE

# Paraneoplastic dermatomyositis accompanying nasopharyngeal carcinoma: Diagnosis, treatment and prognosis

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## KEYWORDS

Dermatomyositis;  
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**Summary** Dermatomyositis (DM) is a multisystem inflammatory disorder primarily affecting the skin and muscles. Its pathophysiology is still very poorly understood, but humoral and cellular immune dysregulation is apparent. Diagnosis of DM is based on five criteria: proximal limb muscle weakness, serum muscle enzyme elevation, histopathologic muscle abnormalities on muscle biopsy, electromyographic abnormalities, and clinical inflammatory dermatological manifestations (heliotrope rash, poikiloderma, and inflammatory lesions on the hands and facing joints). DM is frequently associated with certain cancers, and may appear before, concurrent with, or after diagnosis of cancer. DM has been reported to be associated with approximately one per 1000 cases of nasopharyngeal carcinoma. Treatment is based on long-course nonselective immunosuppression, particularly corticosteroids, by general route, even when malignancy is present, but new-targeted therapies may modify the treatment strategy in the near future. Despite iatrogenic immunosuppression, the prognosis of nasopharyngeal cancer is not worse in patients with paraneoplastic DM. We report one case as an illustration of this paraneoplastic course (evolving in parallel with the cancer), and to make an update on the state of knowledge on paraneoplastic DM in such cancers.

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## Introduction

Dermatomyositis (DM) is a multisystem inflammatory disorder primarily affecting the skin and muscles. Its pathophysiology is still poorly understood. It is associated with malignancy in 18–32% of cases, appearing before, simultaneously with, or after the diagnosis of cancer [1] DM may

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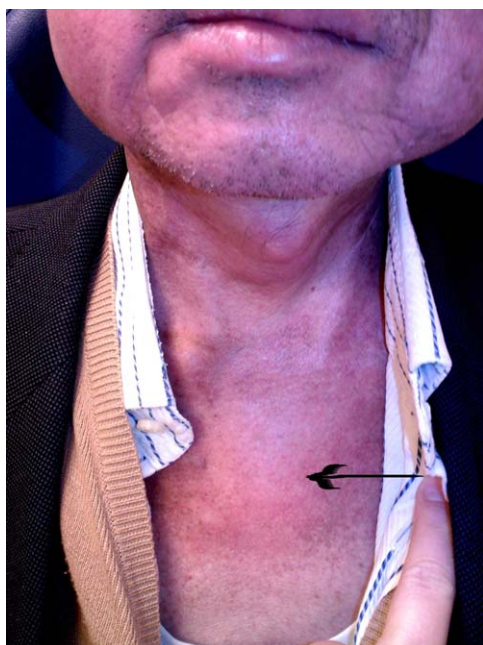
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parallel the course of the disease, with a paraneoplastic course, or show an independent course. DM is more strongly associated with ovarian, lung and digestive tumors, but has also been reported in association with nasopharyngeal carcinoma (NPC), particularly in the Southeast Asian population, although the incidence of this association is less than 1/1000 cases of NPC, and less than 200 cases have been reported in the literature [2]. The aim of the present study is to report a case of paraneoplastic DM associated with nasopharyngeal cancer, and to illustrate the diagnostic, therapeutic and prognostic aspects of this entity, of which, despite its rarity, clinicians treating NPC should be aware.

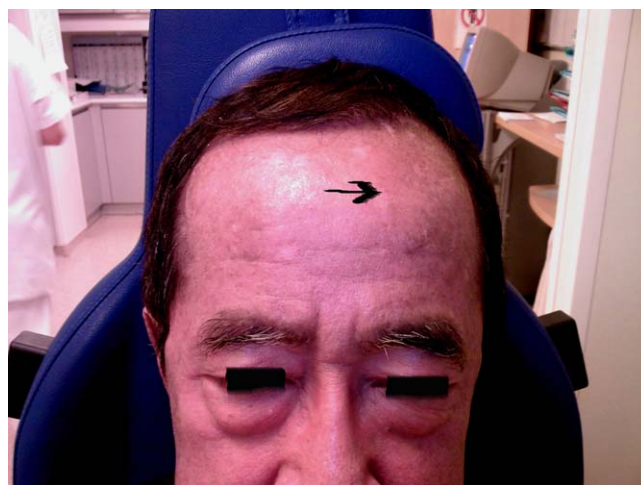
## Case report

A 58-year-old male, born in Cambodia and living in France since early adulthood, without previous medical history, was referred to the Department of ENT Head and Neck Surgery for treatment and diagnostic work up for epistaxis. A nasopharyngeal mass was observed endoscopically. No clinically palpable neck mass was noted. However, dermatological abnormalities that had recently appeared were noted: a rash on photoexposed areas (Fig. 1) with edema along the eyelid margin (Fig. 2), and poikiloderma on the neck and the upper chest, with inflammatory and erosive lesions on the arms. Imaging and pathological staging led to diagnosis of an undifferentiated carcinoma of the nasopharynx (NPC, World Health Organization type III), stage T3, N1, M0 (one retropharyngeal lymph node) [3].

Treatment consisted of cisplatin and 5-fluorouracil concomitant with external beam radiation therapy (64 Grays). Three weeks into treatment, the patient developed erythematous plaques on his hands, particularly around the nails, and complained of disseminated myalgia, proximal muscle weakness and dyspnea with dysphagia. On physical examination, muscle strength was normal. Dysphagia was attributed



**Figure 1** Heliotrope rash.



**Figure 2** Rash on forehead and periorbital edema.

to the radiation therapy. Enzymatic testing showed an increase in creatine kinase (3198;  $N < 195$ ), aldolase (24.9;  $N < 7.6$ ) and lactate dehydrogenase (716;  $N < 400$ ). Antinuclear, anti-Jo-1 and anti-Ro (SS-A) antibodies were negative. The diagnosis of DM was based on the clinical characteristics and biological findings, and the association with malignancy.

Treatment with 1 mg/kg bodyweight prednisone was given as initial therapy, but there was progressive increase in muscle weakness with associated dysphagia. The treatment was therefore intensified by the adjunction of high-dose intravenous immunoglobulins, which gave complete regression of the muscular and cutaneous symptoms. Low-dose maintenance therapy with prednisone was continued, and the patient was followed up in the dermatology clinic every month and underwent a clinical head and neck examination every 2 months.

Six months after terminating radiation therapy, the patient presented worsening of his cutaneous disease, which was treated with hydroxychloroquine. ENT examination and MRI of the nasopharynx were normal but  $^{18}\text{F}$ FDG-PET/CT showed uptake in a left level-II lymph node (subdiaphragmatic node). The patient underwent modified radical neck dissection, and pathology confirmed a lymph node metastasis of the NPC with extracapsular extension. Adjuvant chemoradiotherapy re-radiation was performed, and gave clinical, radiological and PET/CT remission with complete remission of DM.

The patient was disease-free until 14 months later, when the cutaneous manifestations of DM reappeared. Tumor recurrence was suspected, and a complete work-up found a solitary lung nodule in the upper right lobe. Transthoracic biopsy showed a pulmonary metastasis of NPC, which was treated surgically, as the metastasis was single. Pathologic analysis confirmed the biopsy findings and also found histoplasmosis in adjacent lung tissue. Ketoconazole treatment was initiated. The symptoms related to DM improved, but cutaneous signs on the face and hands persisted.

Eight months following surgery, routine PET/CT found new lung metastases associated with a 3 cm mediastinal lymph node metastasis. Six cycles of chemotherapy (docetaxel, cisplatin, 5-fluorouracil) were administered.

The patient was still alive with disease, 5 years after initial diagnosis.

## Discussion

NPC accounts for less than 1% of all malignancies and affects approximately one person in 100,000 in North America and Western Europe, but is more frequent in Asia and North Africa, affecting five to nine per 100,000 of the population [4]. It is particularly frequent in southern China, totaling almost one-third of all malignancies treated, according to Hu et al. [2] It is characterized by the frequency of an undifferentiated pathological subtype, its relationship to Epstein-Barr virus with viral DNA detectable in tumor cells, a high metastatic potential and frequent association with paraneoplastic syndromes such as fever, clubbing osteoarthropathy and leukemoid reactions [5].

DM is an idiopathic inflammatory myopathy with prominent and often characteristic cutaneous manifestations. Patients commonly present with cutaneous disease accompanied or shortly followed by proximal muscle weakness. In the absence of cutaneous disease, the process is known as polymyositis (PM) [6,7] Bohan and Pete [8] suggested the use of five criteria to define DM-PM: (1) progressive, symmetrical weakness of proximal limb muscles and anterior neck flexors; (2) dermatological signs (heliotrope rash with periorbital edema, Gottron's papules (scaly dermatitis on the joints of fingers), dermatitis on elbows, knees or feet; (3) muscle biopsy with necrosis of type 1 and 2 fibers, phagocytosis, perifascial atrophy, inflammatory exsudate, and other features; (4) elevated muscle enzyme levels (especially CPK, aldolase and LDH); (5) a particular electromyographic triad of signs. The presence of three or four criteria plus the rash is diagnostic for DM, and only two criteria plus the rash are highly suggestive of DM.

DM may be idiopathic, especially in children, but is also commonly related to malignancy. In the epidemiological study by Hill et al., 32% of DMs were associated with cancers of the ovary, lung, pancreas, breast or gastrointestinal tract or non-Hodgkin's lymphoma [1]. Since the first observation of NPC associated with DM in 1969, more than 160 cases have been reported [9]. The association is rare in Caucasians [10–12] but not uncommon in the Far East and North Africa [2,9,13–16]. Chan reported a series of DM cases in Singapore, 41% of which were associated with malignancy, with 60% of the latter being NPC [17]. Hu et al. performed a statistical study of DM with malignancy in China and found an incidence of 20.3%, 78.4% of which were NPC; DM was associated in 0.086% of cases of NPC [2].

The pathogenesis of DM is still poorly understood and several mechanisms have been suggested. Histologically, immune complex deposition is seen at the dermal-epidermal junction. There is an increase in CD4 T cell and B lymphocyte levels, and this inflammatory infiltrate is predominantly seen in the perivascular regions. Capillary obliteration, fibrin thrombi and endothelial cell damage are hallmarks of DM [18]. One theory of the association seen between DM and malignancy is that tumors express oncoproteins that stimulate an immune response, and auto-antibodies are deposited in the skin and muscle where similar antigens may be present. About 30% of patients with DM have

myositis-specific antibodies. Three different types of antibodies have been recognized: anti-synthetases, anti-signal recognition particle antibodies and anti-Mi-2 antibodies [19,20] More recently, the role of type 1 interferons in the development of both muscular and dermatological manifestations has been shown [21]. A direct relationship between EBV and DM has not been demonstrated. Yamashita, in a case report of EBV-associated gastric cancer in a patient with DM, however, speculated that EBV-associated gastric cancer caused DM as a paraneoplastic syndrome and that EBV may somehow play a role [22]. Like other autoimmune disorders, DM shows a high incidence of HLA-DR3 and HLA-B8 in human leukocyte antigens [23,24]. Tumor necrosis factor alpha and B lymphocytes also seem to play major roles in the pathophysiology of DM, but the exact involvement of each in the immune system remains to be elucidated [25,26].

The treatment of DM in a patient with cancer involves treating the DM and treating the malignancy. The treatment of DM is the same in patients with or without associated malignancy, and *mutatis mutandis* for the tumor. The goal of therapy in DM is to enhance muscle strength and to improve extramuscular manifestations. There have been very few controlled clinical trials. Treatment remains largely empiric, using agents that are non-selective in their effects on the immune system [27–30]. Topical emollients and steroids are important for all patients, and may control the skin lesions symptomatically until the tumor itself is treated and the DM regresses. If the tumor cannot be treated quickly and radically, then the patient will probably require oral corticosteroids [31].

High-dose intravenous immunoglobulin has shown to be beneficial for recalcitrant DM [20,32]. Hydroxychloroquine is quite effective in about 80% of DM patients when used as a steroid-sparing agent [33]. Immunosuppressors, such as methotrexate, azathioprine or cyclosporin, may be effective in inducing or maintaining remission [34–36] Theoretically, these immunosuppressant drugs could exacerbate malignancy, although this does not seem to be the case in practice. EBV-associated lymphomas have been reported in DM patients treated with immunosuppressants [37,38] but to our knowledge no case of secondary lymphoma in a patient with both DM and malignancy has been reported. Most recently, rituximab, a monoclonal antibody directed against the surface antigen CD20 present on most B lymphocytes, and used to treat B-cell lymphomas and some severe forms of lupus and rheumatoid arthritis, has been suggested for use in DM, following a case report of its efficacy [26].

Many authors have reported that, after complete remission following radiation therapy for NPC, the symptoms and physical signs of DM disappeared or improved, with relapse of DM correlating to locoregional recurrence or detection of metastases. Usually the activity of DM mirrors that of the malignancy. When the patient enters a period of cancer remission, their DM activity can be used to monitor for early relapse [39]. There is, however, a subset of cases where DM does not reflect the treatment and response of the malignancy [31]. Hidano et al. reported that, in their series of patients, most of the malignancies were temporally related to the DM, and that 37.3% of the patients improved following cancer surgery [40]. Cox et al. also reported patients who showed improvement in their DM with tumor resection and DM relapses concurrent with recurrent tumor [41]. This was



noted in our present patient, in whom every relapse of DM was followed by the discovery of a metastasis of the NPC. In treated patients, side-effects of radiation therapy, such as dysphagia or skin pigmentation, may mimic a relapse of DM, so that other cutaneous and muscular signs and symptoms must be found to confirm relapse.

The prognosis of NPC with DM has not been shown to be different from NPC in general, despite immunosuppressive therapies. In Hu et al.'s case-control study of 90 patients, actuarial survival at 5 and 10 years was 50% and 34.5% respectively for the group of NPC patients with DM versus 57% and 55% respectively for the group of NPC patients without DM, which was not statistically significant [2].

## Conclusion

NPC with paraneoplastic DM is a rare but specific entity. The diagnosis of DM is based on clinical findings, abnormal muscular enzyme titers and negative auto-antibody testing. The course of DM may follow that of the NPC, but may also evolve independently of the cancer. Side-effects of radiation therapy may aggravate the symptoms of DM, such as dysphagia and skin inflammation, and may also mimic a relapse of DM in treated patients. The association of DM with NPC does not seem to influence the prognosis of the cancer, despite the long-term immunosuppression necessary in these patients, so that both affections should be treated accordingly and independently by the corresponding specialists.

## Conflict of interest statement

None.

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